Remarks

Claims 1-58 are currently pending in the application. Claims 1-27 and 31-58 currently stand rejected. Claims 28-30 are objected to. Claims 38, 39, 49, 50, and 55 are cancelled by the present amendment. Claims 37, 40, 41, 43, 47, 48, 54, 56, and 57 are amended. New claim 59 is added. Applicant respectfully submits that no new matter is added by the present amendment of the claims. The rejections levied in the Office Action are addressed below.

Rejections under 35 U.S.C. § 112

Claim 47 is rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite. The Examiner noted that claim 47 incorrectly recited "QS-21" as a species of the bacterial or liposomal adjuvants of claim 46. Applicant thanks the Examiner for pointing out this inadvertent error. New dependent claim 59 has been introduced to recite QS-21 as a saponin adjuvant. Applicant requests that the rejection be removed.

Claims 1-27 and 31-58 are rejected under 35 U.S.C. § 112, 1st paragraph. Specifically, the Examiner asserts that the specification "does not reasonably provide enablement for clustered constructs of claim 1 conjugated with carriers that are not the [Pam_3Cys] lipids, such as KLH, polylysine, HSA, or BSA, pharmaceutical compositions comprising the clustered constructs of claim 1 in combination with an immunogenic carrier which is not the above lipid, or methods of treating cancer comprising the administration of the cluster constructs of claim 1, without the [Pam_3Cys] lipid and without a saponin adjuvant." Applicant respectfully disagrees.

The chemistry of protein/peptide/polypeptide conjugation to carrier proteins is well developed and familiar to one of ordinary skill in the art. Thus, the skilled artisan would know how to conjugate an inventive glycopeptide to KLH, polylysine, HSA, or BSA. Furthermore, Applicant respectfully submits that the present specification has appropriate guidance with respect to such conjugation chemistries.

Applicant respectfully submits that the Examiner has failed to meet her burden in levying a lack of enablement rejection. It is well settled that, "In order to make a

rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)...A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is *a reason to doubt* the objective truth of the statements contained therein which must be relied on for enabling support." (see MPEP 2164.04, emphasis added).

The specification provides, for example, a general description of crosslinking heterobifunctional reagents on page 26 of the Appendix to the Specification under the heading "carrier protein hapten/peptid/polypeptide conjugates for use as immunogens." A description of a glycoaldehyde-based conjugation to KLH is described throughout the specification (see pages 81-82, paragraph [0195]; Example 1; page 102, paragraph [0246]; and Figures 6, 8, and 12), and a related method employing a (4-(maleimidomethyl) cyclohexane-1-carboxyl hydrazide) (MMCCH) crosslinking reagent is described on pages 96-97, paragraphs [0223]-[0232].

A description of conjugation to KLH via a maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) crosslinking reagent is described on pages 129-130, paragraphs [0311]-[0312] and Figures 19, 22, and 23. Applicant respectfully submits that one of ordinary skill would be able to take the thiol of Figure 34 and apply the chemistry shown in figure 23 and described on pages 156-157, paragraph [0378]. Applicant has provided sufficient disclosure to enable clustered constructs of claim 1 conjugated with carriers such as KLH, polylysine, HSA, or BSA, and requests that the rejection be removed.

The Examiner states that "the specification does not teach an alternative use for the constructs which are not linked or provided with the [Pam_3Cys] lipid carrier other than as vaccines against cancer." Applicant respectfully submits that constructs that are not yet conjugated to an immunogenic carrier (*e.g.*, R is hydrogen) are useful as intermediates in the preparation of conjugated products.

The Examiner asserts that "the specification provides no teaching regarding the 'spacer' other than those which are peptidic in nature." The Examiner states that Kudryashov *et al.* (PNAS, **2001**, *98*, 33264-3269) teaches that administration of clustered epitopes of a Le^y-KLH conjugate to mice resulted in antibodies which only recognized the immunizing epitope and did not recognize isolated Le^y. However, when clustered epitopes of a Le^y-Pam_3Cys conjugate were administered with QS21, the elicited antibodies recognized isolated Le^y better than clustered $(Le^y)_3$. The Examiner then concludes that "one of skill in the art would conclude that the properties of the conjugate could be altered in an unknown manner by using spacers which are not peptides because the immune response is sensitive to carrier structure and therefore it would be expected that the immune response would be sensitive to the structure of the spacer as well." Applicant respectfully disagrees.

As an initial matter, Applicant submits that the reactivity of immunogenic carriers is completely irrelevant to the spacer of the present claims. While immunogenic carriers are expected to provoke an immunogenic response – and not necessarily identical responses – there is no teaching by Kudryashov *et al.* that modifications to the peptide backbone (*i.e.* "spacer") have a measurable effect on the immunogenicity of the constructs. In fact, Kudryashov *et al.* teach the opposite. By testing constructs with an α-O-GalNAc Ser linkage and those linked through an unnatural β-O-GalNAc Ser linkage, Kudryashov *et al.* found that "both antigen species were equally efficient at producing antibodies to natural forms of Le^y and cells" (see page 3268, first full paragraph). Thus, since it appears that the carbohydate structure itself can serve as the epitope, it is unclear on what basis the Examiner is asserting her claim that the immune response would be sensitive to the structure of the spacer. Applicant requests that the rejection be removed.

The Examiner further finds that "one of ordinary skill would not know how to use the broadly claimed clustered construct which only functioned to elicit antibodies to the immunizing antigen and did not provide any cross reacting antibodies the bind to cancer cells expressing the antigen." Applicant is puzzled by the Examiner's comment. As an initial matter, Applicant is unsure of the basis for the Examiner's assertion that non-cross reactive antibodies would be obtained. The Examiner seems to imply that such a

conclusion could be drawn from Kudryashov *et al.*, as if Kudryashov *et al.* had found such non-cross reactive antibodies.

On the contrary, Kudryashov *et al.* found that antibodies induced by both Pam_3Cys *and* KLH conjugates bind to tumor cells. That is, sera from mice immunized with either the Pam_3Cys or KLH conjugate reacted with Le^y-positive tumor cells (see page 3266, Table 1). Thus, despite any differences between these carriers in the reactivity of elicited antibodies to isolated Le^y or clustered $(Le^y)_3$, both carriers resulted in antibodies that bind tumor cells and, in the case of Pam_3Cys, an adjuvant was unnecessary. Kudryashov *et al.* concludes "these results may be indicative of *subtle* differences in the way that Le^y is displayed on a cell surface in contrast of display in a plastic surface assay" (emphasis added). There is certainly no indication that one could achieve only non-cross reactive antibodies. Thus, the Examiner has failed to establish a reasonable basis to question the enablement provided for the claimed invention (*e.g.*, claims 54 and 56 that recite antibodies that bind with tumor cells).

Moreover, one of ordinary skill reading the present specification would appreciate that non-cross reactive antibodies could indeed be useful, among other things as reagents to characterize the structure of clustered conjugates.

For all of these reasons, Applicant respectfully requests that the rejection be removed.

Miscellaneous Amendments

Applicant has amended claims 37, 48, 54, and 56 to introduce an immunogenic carrier.

Claims 40, 41, and 43 are amended to correct claim dependencies.

In view of the foregoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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